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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/756,411	01/08/2001	Franco Lori	NIH061.1CP1C2	5460

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KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
CRANE, LAWRENCE E	

ART UNIT	PAPER NUMBER
1623	15

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/756,411	Applicant(s) Lori et al.	
	Examiner L. E. Crane	Group Art Unit 1623	

- THE MAILING DATE of this communication appears on the cover sheet beneath the correspondence address -

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE --3-- MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be filed after six months from the date of this communication.
- If the prior for reply specified above is less that thirty (30) days, a reply within the statutory minimum of thirty days will be considered timely.
- If NO period for reply is specified above, such period shall ,by default, expire SIX (6) MONTHS from the date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 USC §133).

Status

[X] Responsive to communication(s) filed on -04/07/03 (RCE, Response & 2 Declarations/Exhibits)-.
[] This action is **FINAL.**
[] Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

[X] Claims ---21-30--- are pending in the application. Claims -[]- have been cancelled.
Of the above claim(s) ---[]--- is/are withdrawn from consideration.
[] Claim(s) ---[]--- is/are allowed.
[X] Claims ---21-30--- are rejected.
[] Claim(s) ---[]--- is/are objected to.
[] Claim(s) ---[]--- are subject to restriction or election requirement.

Application Papers

[] See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
[] The proposed drawing correction, filed on -[]- are [] approved [] disapproved.
[] The drawing(s) filed on -[]- is/are objected to by the Examiner.
[] The specification is objected to by the Examiner.
[] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119(a)-(d)

[] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119 (a)-(d).
[] All [] Some* [] None of the CERTIFIED copies of the priority documents have been
[] received.
[] received in Application No. (Series Code/Serial Number) -[]-.
[] received in the national stage application from the International Bureau (PCT Rule 17.2(a)).
* Certified copies not received: -[]-.

Attachment(s)

[] Information Disclosure Statement(s), PTO-1449, Paper No(s). ---[]---
[X] Notice of Reference(s) Cited, PTO-892
[] Notice of Draftsperson's Patent Drawing Review, PTO-948
[] Interview Summary, PTO-413
[] Notice of Informal Patent Application, PTO-152
[] Other: -[]-.

No claims have been cancelled, no claims have been amended, and no new claims have been added as per the Response filed April 7, 2003. Two declarations filed under 37 C.F.R. §1.132 with Exhibits filed April 7, 2003 have also been received and made of record.

Claims **21-30** remain in the case.

Claims **21-30** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims **21-30** are directed to pairs of compounds, the specific chemical identities of which either have not been specified or have been only specified in part, and are therefore claimed more broadly than is supportable by the instant disclosed exemplification.

Applicant's arguments filed April 7, 2003 have been fully considered but they are not persuasive.

Citing Dr. Vila's declaration, applicant argues as follows: "... in view of the combination of hydroxyurea, a ribonucleotide reductase inhibitor, and ddI, a nucleoside reverse transcriptase inhibitor (NRTI), it is obvious that this principle should be viable for the combination of other NTRI's, and that any modality that would deplete the intracellular pool of deoxynucleotide phosphates could substitute for hydroxyurea." Examiner considers this argument to be nothing more than speculation which, in light of the references supplied as exhibits, is not a convincing argument in support of applicant contention that the instant written description is sufficient. Examiner refers in particular to Exhibit No. 6 (PTO-1449 ref.

53) wherein Malley et al., in confirmation of the Malley et al. '161 patent's findings, disclose at page 11019 in Figures 2B and 3B that the **only** combinations of active ingredients which are active against HIV in an "activated" *in vitro* cell culture at concentrations compatible with human administration are i) ddI and hydroxyurea or ii) ddI and D-aspartic acid hydroxamate (DAH), while other combinations of two very well known NTRI's (AZT & ddC) with hydroxyurea or DAH failed to produce a similar effect. In addition, Malley et al., at page 11017, column 1, 2nd paragraph following the Abstract, state the following warning: "... it is far from clear that the sensitivity of HIV to drugs as assessed *in vitro* in long-term dividing cell lines and phytohemagglutinin (PHA)-stimulated mononuclear cells accurately reflects the virus-drug response in patients with HIV infection," and then notes that AZT, ddC and ddI, when administered alone, are active in inhibiting HIV *in vitro*, but " ... are only partially effective in suppressing viral replication in patients with AIDS," with the following sentence noting that AZT administration does not appear to have any effect on either the length or ultimate outcome of AIDS infections. Examiner therefore concludes that the instant art area was highly unpredictable in 1994, that it remains highly unpredictable today, and for this reason examiner remains convinced that extrapolation beyond the findings of Malley and Vila is not presently possible in the absence of test data to support this extrapolation. In summary, examiner finds the Malley reference data noted above to be an effective counterweight to applicant's request for a finding of patentability in the absence of a clear showing that the ddI/hydroxyurea combination is not the solitary working exemplification of applicant's hypothesis; i.e. the written description problem is not effectively addressed by the Vila declaration.

Applicant's arguments filed September 4, 2002 have been fully considered but they are not persuasive. (Repeated to insure a complete record in this document.)

The noted claims have not met the written description standard of *Regents of the University of California v. Eli Lilly* (119F.3d 1559 at 1568; 43 USPQ2d 1398 at 1406 (Fed. Cir 1997)) which MPEP §2163 at page 2100-162, column 1, quotes as follows: "A definition by function alone 'does not suffice' to describe a coding sequence 'because it is only an indication of what the gene does, rather than what it is.'" Applicant continues to rely on generic functional terminology including "an inhibitor of ribonucleotide reductase" and "an antiviral nucleoside phosphate analog other than a thymidine or cytidine analog," wherein the disclosure definitions thereof does not overcome the functionality of the noted terms.

Claims **21-30** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims **21-30** are only enabled by the combination of hydroxyurea and 2',3'-dideoxyinosine. With only a single example of efficacy demonstrated, examiner is unable to agree that the single example that works is supportive of extrapolation to other examples which are only prospective without additional evidence in support of such an extrapolation. Examiner notes the opinions of other authorities, but must rely on US precedent including *Ex parte Balzarini et al.* 21, USPQ 2d 1892, 1894 (BPAI, 1991) which in its first opinion stands for the

proposition that claims directed to medicinal treatments of diseases in highly unpredictable art areas are properly rejected under 35 U.S.C. §112, first paragraph as lacking adequate enablement, in the absence of sufficient test data in support of the efficacy of the alleged treatment. See MPEP at 2107.03 (p. 2100-44, col. 2, in the August, 2001 revision).

Applicant's arguments filed April 7, 2003 have been fully considered but they are not persuasive.

The Balzarini case, cited herein and accepted by applicant as the appropriate standard herein, involved claims directed to a method of treating HIV with compounds which "looked like AZT," but for which there was no test data whatsoever to support the asserted method of treating. The instant case is somewhat different because first, there is some *in vitro* data, and second, there is a question concerning whether extrapolation of in vitro test data adequately supports claims directed to *in vivo* HIV treatment (see response to previous grounds of rejection; Malley et al., PTO-1449 ref. **53**). The instant response argues citing the Vila declaration that the instant claims are adequately enabled under the Balzarini standard because tests conducted under quiescent conditions (ala Malley et al. '161) are deemed to be a near equivalent in their predictive value to tests data from activated cell cultures including those cited herein. Examiner respectfully disagrees and notes that the Malley et al. reference (Exhibit 6) shows a result similar to that of the Malley et al. ;161 patent, namely that only ddI plus a hydroxamate or ddI plus hydroxyurea are effective in inhibition of HIV in vitro. And, to recapitulate the argument in response following the previous rejection, combinations of other very well known NRTI's with hydroxyurea or DAH do not display the same activity. Therefore, applicant's hypothesis that extrapolation from the successful ddI/hydroxyurea combination pioneered by Malley et al. '161 to all other possible combinations is

i) lacking adequate factual support in the prior art, and
ii) lacking adequate support from experimental data found herein. Applicant's limitation excluding thymidine and cytidine analogues is noted, but is not found to be sufficient in the absence of a clear and convincing showing that the ddI/hydroxyurea findings in Malley et al. '161 do not represent a singular phenomenon. For this reason the instant grounds of rejection are deemed to remain valid and therefore have been maintained.

Applicant's arguments filed September 4, 2002 have been fully considered but they are not persuasive. (Repeated to insure a complete record in this document.)

Examiner has reviewed pages 24-25 and Table 7 at page 26 and, because of the repeated use of terms like "expected," has come to the conclusion that the disclosure of Table 7 is entirely prospective for all combination therapies except that of hydroxyurea plus ddI, a finding of **Malley et al. '161**, PTO-892 ref. **E**.

Claims **21-30** are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims **21-30** are rejected under 35 U.S.C. §112, second paragraph, as being indefinite in that they fail to point out what is included or excluded by the claim language. These claims are omnibus claims.

Applicant's arguments filed April 7, 2003 have been fully considered but they are not persuasive.

Applicant argues that the instant claims are not "omnibus" claims. Examiner quotes as follows from the MPEP §2173.05(r): "This [omnibus]

claim should be rejected under 35 U.S.C. §112, second paragraph because it is indefinite in that it fails to point out what is included or excluded by the claim language." Examiner has reviewed the claims and, although the particular phraseology of the classical omnibus claim is not found therein, it is clear to examiner that the functional language of each of the noted functional terms ("an inhibitor of ribonucleotide reductase" and "an antiviral nucleoside") "... fails to point out what is included or excluded by the claim language." Therefore, examiner respectfully disagrees and finds that the instant claims, by its reliance on these terms, is in effect an omnibus claim because each of said terms may be read to say -- a compound or active ingredient substantially as shown and described --. Therefore, the instant grounds of rejection has been maintained.

In each of claims **21-30** one or both of the active ingredients have not been specified with other than with functional language, and therefore each noted claim lacks properly defined metes and bounds because the ordinary practitioner cannot determine what is included or excluded, or what was included or excluded at the time of filing.

Applicant's arguments filed April 7, 2003 have been fully considered but they are not persuasive.

Applicant argues that "[t]he phrases 'an inhibitor of ribonucleotide reductase' and 'an antiviral nucleoside' are as accurate as the subject matter permits, such components of a mixture being undefinable by 'chicken wire' structural formulas known to organic chemists." Examiner respectfully disagrees, and respectfully refers applicant to class 514, subclasses 44-51 and in class 536, subclass 23.1, wherein there are many patents which have effectively claimed subject matter using "chicken wire" formulas including some very complex nucleic acid

analogues. The assertion that applicant is unable to devise a "chicken wire" formulation for the instant claimed subject matter is unfortunate because this appears to leave only one alternative, limitation to the chemical names of the active ingredients listed in the specification. And the assertion that the noted terms are "as accurate as the subject matter permits" is deemed to be an inadequate reason. Applicant is encouraged to hire an organic chemist to assist in determining what chemical formulas may be introduced into the claims as replacements for the noted terms. In conclusion, examiner is not prepared to permit functional language of the kind noted in a claim as a definition of an active ingredient, and therefore the instant grounds of rejection has been maintained.

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam,* 686 F. 2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir 1985); and *In re Goodman,* 29 USPQ 2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. §1.78(d).

Effective January 1, 1994, a registered attorney or agent or record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. §3.73(b).

Applicant's arguments filed April 7, 2003 have been fully considered but they are not persuasive.

Applicant has acknowledged the possible appropriateness of the instant rejection has not provided an appropriate terminal disclaimer.

Claims **21-30** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims ***12-22*** of U.S. Patent No. **6,046,175** (PTO-892 ref. **H**). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are directed to a binary composition which includes two active ingredients generically defined in a manner which includes the subject matter previously claimed.

Applicant's arguments filed April 7, 2003 have been fully considered but they are not persuasive.

Applicant has acknowledged the possible appropriateness of the instant rejection has not provided an appropriate terminal disclaimer.

Claims **21-30** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims ***3-8*** of U.S. Patent No. **6,194,390** (PTO-892 ref. **J**). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are directed to a method of treating HIV in a human host wherein the active ingredients are defined

generically in a manner which includes the subject matter of the previously patented claims.

Applicant's arguments filed April 7, 2003 have been fully considered but they are not persuasive.

Applicant has acknowledged the possible appropriateness of the instant rejection has not provided an appropriate terminal disclaimer.

Claims **21-28** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims *1-3* of U.S. Patent No. **5,521,161** (PTO-892 ref. **E**). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are directed to a method of treating HIV in a human host wherein the active ingredients are defined generically in a manner which includes the subject matter of the previously patented claims.

Applicant's arguments filed April 7, 2003 have been fully considered but they are not persuasive.

Applicant has acknowledged the possible appropriateness of the instant rejection has not provided an appropriate terminal disclaimer.

Claims **21-30** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims *1-3* of U.S. Patent No. **5,736,527** (PTO-892 ref. **G**). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are directed to a method of treating HIV in a human host wherein the active ingredients are defined generically in a manner which includes the subject matter of the previously patented claims.

Applicant's arguments filed April 7, 2003 have been fully considered but they are not persuasive.

Applicant has acknowledged the possible appropriateness of the instant rejection has not provided an appropriate terminal disclaimer.

Claims **21-30** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims ***6-8*** of U.S. Patent No. **6,093,702** (PTO-892 ref. **K**). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are directed to a binary composition which includes two active ingredients generically defined in a manner which includes the subject matter previously claimed.

Applicant's arguments filed April 7, 2003 have been fully considered but they are not persuasive.

Applicant has acknowledged the possible appropriateness of the instant rejection has not provided an appropriate terminal disclaimer.

In view of applicant's filing of an RCE, this rejection has not been made final to provide additional time for applicant to formulate a response.

Papers related to this application may be submitted to Group 1600 via facsimile transmission(FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone numbers for the FAX machines operated by Group 1600 are **(703) 308-4556** and **703-305-3592**.

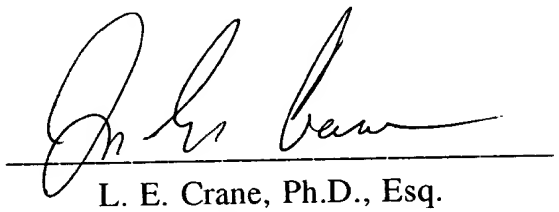
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E.

Crane whose telephone number is 703-**308-4639**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson, can be reached at (703)-308-4624.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is 703-**308-1235**.

LECrane:lec
05/02/03



L. E. Crane, Ph.D., Esq.
Patent Examiner
Technology Center 1600